CORONARY HEART DISEASE

Heart disease is one of the leading causes of death in many countries and, perhaps as a result, it has been the subject of intensive scientific study for many years. Although much has been learned during this time, the causes of heart disease are not known. Nevertheless, based primarily on statistical reports, claims are often made that cigarette smoking is a major cause of diseases of the heart, in particular coronary heart disease (CHD), which occurs when the heart does not receive enough oxygen.

Despite such allegations, the literature on CHD demonstrates that there is much that is unknown about what role, if any, smoking may play in its development. In fact, a group of United States physicians recently concluded that when the literature on tobacco and CHD is reviewed critically, "a number of perplexing and as yet unresolved paradoxes painfully surface."[1] For example, although not generally mentioned by anti-smokers, cigarette smoking is only one of many statistical associations, termed "risk factors," that have been reported for heart disease. Others frequently discussed are high blood pressure and elevated blood cholesterol levels. Nor is it generally mentioned by anti-smokers that reductions in such risk factors have not been demonstrated to lead to corresponding reductions in heart disease mortality rates. In addition, there are numerous inconsistencies and anomalies in the epidemiological (population or statistical) studies of smoking and

CHD. Finally, scientists have not been able to establish what, if anything, in cigarette smoke is related to the development of CHD. Accordingly, it is readily apparent that cigarette smoking has not been proven to cause CHD.

Risk Factors

Smoking is often regarded as a risk factor for CHD because smokers are reported to have a statistically increased risk of the disease. However, risk factors do not necessarily imply cause-and-effect. As a literature review from the University of Oslo, Norway, pointed out, "risk factors should not be confused with causal factors."[2] That is because, among other reasons, statistical associations cannot provide information on biological processes whereby a factor, such as smoking, might lead to heart disease.

Most investigators seem to be aware of the limitations of statistical data. Even reports of the United States Surgeon General have recognized this. For example, the first such report, in 1964, noted that "statistical methods cannot establish proof of a causal relationship in an association."[3] Similarly, in the context of discussing smoking and cardiovascular disease, the 1979 report noted that "correlation [association is a type of correlation] is not synonymous with causation."[4] This basic tenet of scientific interpretation, though widely understood, sometimes

seems to be forgotten by antismoking advocates when assessing statistical data concerning smoking and CHD.

It is also important to recognize that smoking is only one of literally hundreds of factors that have been reported to be statistically related to CHD. Some of the most well-known of these, in addition to cigarette smoking, high blood pressure, and elevated blood cholesterol levels, are gender (males are more likely to develop CHD than females), genetics, obesity, physical inactivity, and stress. However, these are only a few of the risk factors that have been reported in the literature, and additional risk factors continue to be reported. One major survey in 1981 listed nearly 250 factors that had been reported to be related to CHD up to that time.[5] An updated review in 1986 noted that an additional 30 to 40 risk factors had been reported since the earlier review and that the literature on risk factors "seems to expand at almost an exponential rate."[6] Although these authors consider smoking to be one of the most important risk factors, whether or which of these may have causal significance is unknown, as the following discussion illustrates.

Genetics

One of the most widely discussed CHD risk factors is genetics or heredity. A number of researchers have speculated that this factor may explain why CHD rates tend to be higher in

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certain families, geographic areas and ethnic groups. The potential role of genetics was considered in detail in two major literature reviews by Drs. Neufeld and Goldbourt, scientists at Israel's Tel Aviv University. In their first review published in 1983, they noted that variations in risk factors, including smoking, could not satisfactorily account for differences in CHD rates in different groups but that genetics play a "significant" role "in determining the degree, time course and severity of the atherosclerotic process and the occurrence of symptomatic CHD."[7] In their second review published three years later, they focused on the genetic aspects of atherosclerosis, a narrowing of the arteries which is often an important underlying condition in the development of CHD. Although they cautioned that "speculations still exceed concrete knowledge" about this disease process, they nevertheless emphasized that genetics is given a potentially important role in its development in the literature.[8]

The apparent importance of genetics in CHD development was also emphasized by the late Philip R.J. Burch, an eminent medical physicist from the United Kingdom's University of Leeds. Based on his analysis of data from several major types of epidemiological studies, he concluded that none of these studies "endorses the idea that the classical 'risk factors' -- except, of course, the familial (genetic) one -- exert any appreciable causal action. Claims to the contrary are based on uncritical evidence and faulty logic."[9]

Stress and Personality

Many studies suggest that people with a certain type of personality are prime candidates for developing CHD. Such persons tend to be hard-driving, time-conscious, often impatient and emotionally tense, characteristics that are likely to promote a stressful lifestyle. No one knows why some persons have such a personality, although it has been speculated that it may have to do with personal preference or some relatively unalterable trait that they are born with. For whatever reason, in most industrialized countries which tend to have the highest CHD rates, many people lead very stressful lives.

One of the most widely discussed aspects of personality in relation to heart disease is the so-called type A versus type B behavior pattern. The pioneers in researching this concept are Drs. Meyer Friedman and Ray Rosenman, who brought these behavior patterns to the attention of the medical community in a 1959 report in the Journal of the American Medical Association. On the basis of their research, they characterized persons with a "type A" behavior pattern as very achievement-oriented, usually toward poorly defined goals, constantly busy, always feeling a sense of urgency about time, alertness and a desire for recognition and advancement. Persons with a "type B" behavior pattern, on the other hand, were generally characterized as having a relative absence of these

characteristics. When Friedman and Rosenman compared the CHD rates of men with "type A" versus "type B" behavior patterns, they found a "startling difference." Men with "type A" behavior were seven times more likely to have heart disease than men with "type B."[10]

Since its introduction, the "type A" concept has been extensively studied and refined by many researchers and investigators. Friedman argues that their findings have strongly confirmed the role of this behavior pattern in CHD.[11] Much of the recent literature in this area has focused on more specific personality and stress-related characteristics that might be part of a broad personality type such as "type A" or "type B." For example, researchers have reported that "hostility,"[12] "time urgency"[13] and "severe anxiety"[14] are associated with CHD.

Reports of what patients say they are experiencing at the time they have a heart attack are consistent with the epidemiological literature associating CHD with personality and stress. For example, an intriguing clinical study from the United States reported that mental stress may, in fact, act as a potential trigger for a heart attack. When nearly 850 heart attack patients were asked about the events that preceded their heart attacks, their most commonly reported potential trigger was "emotional upset."[15]

A possible relationship between behavioral characteristics and CHD has also been supported by the results of animal research. In the United States, an experiment with monkeys at a North Carolina school of medicine reportedly demonstrated that animals exposed to unstable, stressful social conditions had increased development of coronary artery atherosclerosis. The researchers conducting the experiment concluded that these data were "consistent" with "current hypotheses concerning the role of individual behavioral characteristics in the development of coronary disease in humans."[16] In a subsequent study by this same research group, it was reported that monkeys that were relatively more "reactive" to stress as measured by increases in heart rate developed more atherosclerosis.[17] Some animal research reports have even suggested biological mechanisms that might explain how behavioral or personality factors could lead to CHD. For example, Dr. William Gutstein, of the New York Medical College, has reported that electrical stimulation of those parts of the brain that may be involved in the body's response to stress can damage the arteries and induce atherosclerosis.[18]

Intervention Trials

Additional questions regarding the significance of risk factors are raised by the results of risk factor intervention trials. These trials are a type of epidemiological study in which attempts are made to test the theory that reductions in risk

factors, including smoking, will lead to reductions in CHD mortality risk. In such a study, an investigator randomly assigns each participant to either an intervention or a control group. Those in the intervention group receive special assistance in lowering their risk factor levels, for example, to reduce smoking. Their subsequent CHD rates are then compared to those in the control group who did not receive any special assistance.

Despite massive and costly research efforts in numerous countries, intervention trials have failed to establish that lowering risk factor levels reduces CHD mortality risk. The largest of these studies was conducted under the auspices of the World Health Organization in five European countries -- the United Kingdom, Belgium, Italy, Poland and Spain.[19] Other large-scale European trials were performed in Norway[20] and England.[21]

The largest effort undertaken in a single country is the United States' Multiple Risk Factor Intervention Trial, known as MRFIT. MRFIT was designed to examine whether reductions in cigarette smoking, high blood pressure and elevated serum cholesterol would reduce the risk of CHD mortality. Although the participants in the study were successful in reducing the levels of these risk factors, the seven-year follow-up failed to demonstrate that reducing these risk factors significantly reduces the chances of dying from coronary heart disease.[22] Even after a

10-year follow-up, no statistically reliable overall effect on CHD mortality was reported.[23]

Some researchers apparently have had difficulty accepting weaknesses in the intervention trial data. This was a central point in a review of CHD intervention trials by two Irish researchers. James McCormick and Petr Skrabanek, of the University of Dublin, noted that "[d]espite this considerable body of evidence which shows no benefits for intervention, many have interpreted the results as supportive of their wishful thinking."[24] They cited the example of the WHO study which they pointed out showed "no difference" in CHD mortality between the control and the intervention groups, yet the authors attempted to give their reported results public health importance. As McCormick and Skrabanek pointed out, "It would appear that statistical evaluation can be disregarded if it does not support a forgone conclusion."[25]

Viewed together, the risk factor intervention studies represent a variety of different methodologies and study populations. Yet, each one has reported basically similar results -- namely, the failure to demonstrate statistically significant reductions in CHD mortality attributable to reductions in smoking.

Inconsistencies and Anomalies

There are notable inconsistencies and anomalies in many of the studies reporting associations between smoking and CHD. For example, the potential statistical association is sometimes reported to be weak or not even present; trends in CHD rates are not explained by changes in smoking consumption; and studies of CHD rates in exsmokers have serious methodological flaws.

Weaknesses in Association

Some studies do not even report a statistical relationship between smoking and CHD. In Busselton, Western Australia, for example, a large-scale prospective study reported no significant association between CHD and smoking. Although the authors did report that smoking was associated with some disease or mortality outcomes, nevertheless, they commented that smoking "was unrelated to CVD [cardiovascular disease] and CHD in either men or women."[26]

Studies of women, in particular, have raised questions about a statistical association between smoking and CHD. For example, in a prospective study of women in Gothenburg, Sweden, researchers reportedly found "no significant increased risk" of CHD in smoking women.[27] In the United States, even the Framingham Heart Study, perhaps the largest and most well-known prospective

epidemiological study of coronary heart disease risk factors, noted a strong gender difference in any CHD/smoking association. That is, while reports from this study have generally argued for the importance of smoking as a CHD risk factor, it also has been reported that, at least for CHD mortality in women, "no significant relationship can be shown."[28] In fact, on the basis of such apparent gender differences, and on other anomalies in the data, a researcher from Harvard University has suggested that the Framingham Heart Study results in general "are inconsistent with the Surgeon General's views about cigarette smoking and coronary heart disease."[29]

The interpretation of the statistical data on smoking and heart disease is further complicated by reports that this relationship may be observable only in groups with a high fat or cholesterol intake. In fact, the editor of an American medical journal dedicated to the study of the diseases and functioning of the heart has argued that an elevated cholesterol level is the most important factor in the development of heart disease. Although he views smoking as having a role in the development of CHD in individuals with high cholesterol levels, he does not consider it to be an "independent" risk factor.[30] To support this opinion, he cited the experience of the Japanese who are well-known for their low rates of heart disease despite their widespread cigarette smoking, and their low fat and cholesterol diet. Others have also cited the Japanese example as suggesting that cigarette smoking is

"a weak or nonexistent risk factor for heart attack if atherosclerosis from a high cholesterol diet is absent."[31] Obviously, such reported findings must be taken into account in evaluating the literature on smoking and heart disease.

Trends

It is also a statistical paradox that trends in CHD rates over time do not correspond closely with trends in cigarette smoking. In recent decades, for example, CHD rates have reportedly been increasing in some countries and decreasing in others, but such trends have not been shown to be explained by changes in smoking. A report from St. Thomas's Hospital Medical School, in London, for example, observed that since about 1968, CHD mortality has been decreasing in the United States, Canada and some western European countries. However, when these decreases in CHD were compared to changes in fat intake and smoking habits, it was determined that "the change in fat intake rather than smoking habits would appear to be the likely reason for the decline in CHD."[32]

On the other hand, an upward trend in CHD mortality rates was observed in a study of Swedish males during the same time period that their prevalence of smoking decreased. The authors of this study commented that the increase in CHD mortality was apparent in their study, even though "all" the changes in smoking, exercise, and blood pressure treatment that have been used to explain

decreases in CHD mortality in other countries "also apply to Sweden."[33]

Exsmoker Studies

Claims that smoking causes CHD often rely strongly on reports that quitting smoking reduces the risk for this disease. Such claims rely on the assumption that smokers and exsmokers are the same in all respects except for their smoking habits. This is a false assumption, however, as demonstrated by studies from many countries, including Britain,[34] the United States,[35] Japan[36] and Finland,[37] which show that exsmokers differ from smokers in fundamental, even possibly genetic, ways. In fact, those studies show that exsmokers tend to be more like nonsmokers even before they quit smoking.

Perhaps the most comprehensive examination of the characteristics of exsmokers was conducted as part of a large-scale ongoing research project in the United States involving California members of Kaiser Permanente, a private health care insurance plan. In that study, a large number of traits and characteristics including many believed to be related to the development of heart disease were measured in groups of smokers, nonsmokers and exsmokers before the exsmokers quit. It was reported that "smokers who later quit showed statistically significant differences from smokers who continued smoking, in certain cardiovascular symptoms, social and

personal characteristics, smoking intensity, and some other traits."[38]

There is disagreement in the scientific world about the significance of the differences between smokers and exsmokers and how those differences should be interpreted. It has been suggested, for example, that the characteristics of exsmokers put them at a decreased risk of CHD even before they quit smoking.[39] Others have suggested that the characteristics which appear to put exsmokers at decreased risk are "compensated for" by others which may put them at higher risk.[40] These sorts of disagreements indicate the need for further research to obtain a better understanding of the differences between smokers and exsmokers and the possible relationship of those differences to CHD.

Carbon Monoxide and Nicotine

The claim is sometimes made that certain constituents in cigarette smoke, specifically carbon monoxide (CO) and nicotine, have adverse effects on the cardiovascular system. Various theories have been discussed about how these substances could exert an effect. It has been speculated, for example, that both these constituents might increase the rate of the development of atherosclerosis or that they may alter the balance of oxygen supply and demand, thus precipitating angina pectoris (heart pain) or a heart attack. However, despite the intense research to which

tobacco smoke has been subjected over many years, these constituents as found in cigarette smoke have not been scientifically proven to cause coronary heart disease.

Claims that carbon monoxide in cigarette smoke may be involved in the development of CHD have frequently emphasized the early results of a team of Danish researchers.[41] Their research involved exposing rabbits to carbon monoxide for long periods of time and then microscopically examining the arteries to see if any changes had occurred. In their initial studies, they reported vascular changes which they thought were similar to early stages of atherosclerosis in humans. However, when they repeated the experiments (because they thought their initial studies may have been flawed), they were unable to find a toxic effect of carbon monoxide.[42] These and other weaknesses in the data were noted in a subsequent review of a wide variety of literature relating to carbon monoxide from the School of Public Health at the University of Texas Health Science Center, Houston. The review concluded that the concern which has sometimes been expressed about possible effects of CO exposure on the cardiovascular system "is largely unwarranted."[43]

Even the 1983 U.S. Surgeon General's Report, which was the only report to focus exclusively on cardiovascular disease, expressed a number of important reservations about the data on carbon monoxide and nicotine in relation to this disease. For

example, the Report observed that animal experiments on atherosclerosis and carbon monoxide "must be considered to be unsatisfactory."[44] With regard to nicotine, the Report conceded that "the evidence for and against a primary role for nicotine in the development or acceleration of atherosclerosis is not conclusive."[45] Furthermore, it stated that a "mechanism whereby nicotine can trigger a cardiovascular event is unknown."[46]

Similar conclusions were reached in the United Kingdom by an independent scientific committee in a report to the government. Although the committee report asserted that smoking has adverse health effects and that CO and nicotine may be involved, it nevertheless noted several weaknesses in the literature. For example, the report stated that nicotine, at levels in cigarette smoke, "has not been shown to harm the cardiovascular system in healthy people."[47] Regarding carbon monoxide and heart disease, the report noted that the literature has "not clearly established" that it is a causal factor.[48]

Conclusion

Many questions remain unanswered about the possible nature of the role, if any, that smoking may have in the development of CHD. These questions reflect a challenge that only continued research can resolve. Perhaps what is most apparent from the literature is that the causes of heart disease are likely to be

numerous and complicated, and that claims focusing on a single factor, such as smoking, should be regarded with considerable skepticism.

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